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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/835,196	04/13/2001	Barnett S. Pitzele	PHAR 7979/3313US	5348

26648 7590 07/03/2003

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GLOBAL PATENT DEPARTMENT
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EXAMINER	
ZUCKER, PAUL A	
ART UNIT	**PAPER NUMBER**
1621	

DATE MAILED: 07/03/2003

13

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/835,196	PITZELE ET AL.	
	Examiner	Art Unit	
	Paul A. Zucker	1621	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *30 April 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 30 April 2003 has been entered.

Current Status

2. This action is responsive to Applicants' request for reconsideration of 30 April 2003 in Paper No 12.
3. Claims 1-31 remain pending.
4. The rejection under 35 USC § 103 set forth in paragraph 6 of the previous Office Action in Paper No 8 is withdrawn in favor of the new rejections below. Applicants' arguments with regard to this rejection are addressed below.

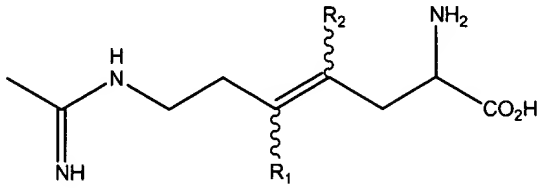
New Rejections

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

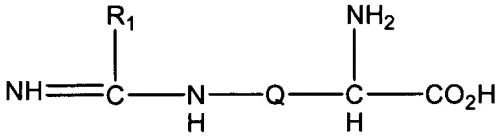
5. Claims 1-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Beams et al (WO 93/13055-A1 07-1993).

Instantly claimed are compounds (geometric and stereoisomers) of Formula (I), where R_1 and R_2 may be H or methyl, or their pharmaceutically acceptable salts :



and pharmaceutical compositions thereof.

Beams teaches (Page 5, line 26-page 7, line 35) a genus of nitric oxide synthase inhibitors of general formula (I):



Where R^1 may be a C_{1-6} straight chain or branched alkyl and Q may be an alkylene, alkenylene or alkynylene group having 3-6 carbons. Beams further teaches (Page 5, line 37-page 6, line 1) optional substitution of Q by one or more C_{1-3} alkyl groups. A preferred embodiment of the compounds is further taught (Page 6 lines 30-36) where Q = $-(CH_2)_vCH=CH(CH_2)_w-$ where v = 0-3; w = 0 to 3; and v + w = 2-4. The instantly claimed compounds correspond to v =2, w =1 and thus fall within the narrow subgenus suggested by Beams. Beams further teaches (Page 7, lines 1-3) a preferred value for R^1 of methyl. Beams teaches (Page 3, lines 23-34) that the genus encompasses all stereoisomeric forms (both E, Z and R,S).

Beams teaches (Page 8, line 14 – page 11, line 4) pharmaceutical compositions of the compounds as well.

Instant claim 28, in particular, (1st and 2nd listed compounds) is obvious over Beams' exemplification (Page 13, lines 23-31, Example 3, and page 15, lines 1-10, Example 8) of (±)-E-2-Amino-6-(1-iminoethylamino)-hex-4-enoic acid, hydrochloride and (S)-Z-2-Amino-6-(1-iminoethylamino)-hex-4-enoic acid, hydrochloride. The 1st and 2nd listed compounds of claim 28 are simply the salts of the adjacent higher homologue with one additional chain methylene unit between the double bond and the amidino group. One of ordinary skill in the art would have had an expectation of similar properties for the instant compounds and those of Beams since they are adjacent homologues. The instantly claimed compounds are therefore *prima facie* obvious over the compounds of Beams.

Thus the instantly claimed compounds and the pharmaceutical compositions containing them would have been obvious to one of ordinary skill in the art. The motivation for the instantly claimed invention would have been to develop other compounds in the genus taught by Beams and apply them, in the compositions taught by Beams, to the methods taught by Beams. The expectation for success would have been near certitude since Beams' genus completely embraces the instant compounds which, Beams' teaches, have the instantly desired activity as nitric oxide synthase inhibitors.

Examiner's Response to Applicants' Arguments with Regard to This Rejection

6. Applicants' have put forth several arguments with regard to this rejection. The Examiner responds to these below:

   a. Applicants argue that Beams does not exemplify the compounds of the invention. The Examiner agrees but points out that Beams exemplifies (Page 14, lines 24-31 and page 15, lines 1-10) the compounds (S)-E-2-Amino-6-(1-iminoethylamino)-hex-4-enoic acid and (S)-Z-2-Amino-6-(1-iminoethylamino)-hex-4-enoic acid over which the compounds of the invention are *prima facie* obvious as adjacent lower homologues. The presumption that homologues are unpatentably obvious is a presumption of fact which places a "burden of persuasion" on the applicant who asserted a contrary fact, *In re Mills* (CCPA 1960) 281 F2d 218, 126 USPQ 513.

   b. Applicants further argue that the addition of a methylene (CH_2) group to ethanol (which is routinely consumed by humans) produces isopropanol which is toxic when consumed in the same manner as ethanol. In response to this argument the Examiner makes two points:

      i. The addition of a methylene group to ethanol has a much more dramatic impact on the properties of ethanol because of its small size and low molecular weight. For example, in the case of ethanol, the addition of a methylene group to produce isopropanol represents a 30.4% increase in the mass of the molecule. In the instant case,

however, the addition of a methylene group to the compound of example 8 of Beams results in an increase in mass of only 7.5%.

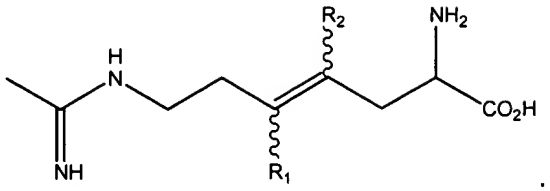
ii. Ethanol and isopropanol, based upon their properties, are clearly not obvious over one another. Applicants, however, have not demonstrated any properties of the instantly claimed compounds that render them unobvious over the compounds disclosed by Beams.

c. Lastly, Applicants argue that the mere disclosure of a chemical species within a genus does not necessarily render it obvious. In the instant case, however, Beams provides clear direction in the exemplification of the compounds (S)-E-2-Amino-6-(1-iminoethylamino)-hex-4-enoic acid and (S)-Z-2-Amino-6-(1-iminoethylamino)-hex-4-enoic acid.

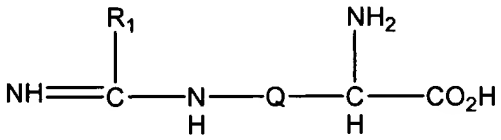
Applicant's arguments filed 30 April 2003 have been fully considered but they are not persuasive for the reasons indicated above.

7. Claims 30 and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Beams et al (WO 93/13055-A1 07-1993).

Instantly claimed are methods for selectively inhibiting the inducible isoform of Nitric Oxide Synthase employing the compounds (geometric and stereoisomers) of Formula (I), where R_1 and R_2 may be H or methyl, or their pharmaceutically acceptable salts :



Beams teaches (Page 5, line 26-page 7, line 35) a genus of nitric oxide synthase inhibitors of general formula (I):



Where the variable groups are as defined at the above-noted location. In particular, Beams' exemplifies (Page 13, lines 23-31, Example 3, and page 15, lines 1-10, Example 8) of (±)-E-2-Amino-6-(1-iminoethylamino)-hex-4-enoic acid, hydrochloride and (S)-Z-2-Amino-6-(1-iminoethylamino)-hex-4-enoic acid, hydrochloride. The instantly claimed compounds (all stereoisomers) with R_1,R_2 = H are simply the adjacent higher homologues with one additional chain methylene unit between the double bond and the amidino group. One of ordinary skill in the art would have had the expectation of similar properties for the instant compounds and those of Beams since they are adjacent homologues. The instantly claimed compounds are therefore *prima facie* obvious those of Beams.

Beams further teaches (Page 16, lines 15 – 25) methods for the selective inhibition of the inducible form of nitric oxide synthase over the constitutive form using the compounds of his invention. Because the instantly claimed compounds are *prima*

facie obvious so are the methods for their use which are precisely coincident with that taught by Beams.

Thus the instantly claimed methods of use would have been obvious to one of ordinary skill in the art. The motivation for the instantly claimed invention would have been to develop other compounds in the genus taught by Beams and apply them, in the compositions taught by Beams, to the methods taught by Beams. The expectation for success would have been near certitude since Beams teaches that his compounds have the instantly desired activity as selective inducible nitric oxide synthase inhibitors.

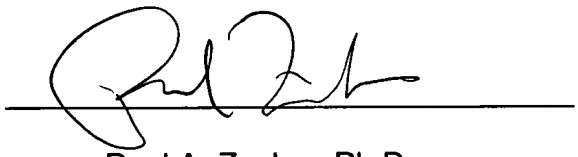
Conclusion

8. Claims 1-31 are pending Claims 1-31 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Paul A. Zucker whose telephone number is 703-306-0512. The examiner can normally be reached on Monday-Friday 7:00-3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann R. Richter can be reached on 703-308-4532. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4556 for regular communications and 703-308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.



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Patent Examiner
Technology Center 1600

July 1, 2003